39. (New) A method according to claim 34 wherein the polypeptide is in the form of a dimer.

40. (New) An isolated polypeptide consisting of amino acids 848-991 of a type F botulinum toxin (SEQ ID NO:2) optionally fused to a polypeptide that facilitates or enhances purification.

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41. (New) A recombinant DNA encoding a polypeptide according to claim 40.--

REMARKS

Reconsideration is requested.

Claims 26, 28 and 31 have been canceled, without prejudice. Claims 34-41 have been added. Claims 5-19, 21, 25, 30 and 32-41 are pending.

Claim 5 has been amended based on the description of the specification on page 5, line 1, for example. The claims are distinguished from disclosures of full-length sequences. Moreover, claim 5 does not recite the amino acid SEQ ID NO:2. New claim 40 however defines polypeptides containing the specific epitopic fragment. The Examiner is urged to appreciate that claim 6 provides a dimer which is not found in the art. Claim 8 has been amended to recite a fusion protein and claims 9 and 10 have been made dependent on claim 8 as is described, for example, at page 6, lines 17-19 of the

specification. Claim 11 has been amended to reflect the amendment of claim 8. Claim 12 has been amended to further define the presently disclosed invention. Claims 34-39 define methods which were previously canceled to advance prosecution. The Examiner apparently did not find the previous amendment in this regard to advance prosecution, and the claims have been added above for completeness.

No new matter has been added.

The specification has been amended as required by the Examiner in paragraph 2 of the Office Action dated October 28, 2002 (Paper No. 29). A copy of the Notice to Comply received with Paper No. 29 is attached. The attached paper and computer readable copies of the Sequence Listing are the same. No new matter has been added. A separate Statement to this effect is attached.

The claims have been amended to obviate the provisional Rule 75 objection to claims 7, 8 and 26 noted in paragraph 4 of Paper No. 29. Reconsideration and withdrawal of the provisional Rule 75 objection of claims 7, 8 and 26 is requested.

The Section 112, first paragraph, rejection of claims 12, 17, 19 and 21 is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following comments.

The Examiner has suggested that because the applicants have failed to demonstrate that the smaller recited fragments are effective as vaccines (they have nothing to do with "fertility" as noted by the Examiner at page 3 of Paper No. 29 and clarification and/or correction of the record in this regard is requested). These are allegedly non-enabled, as the ordinarily skilled worker would not have been able to

define smaller protective epitopes without undue experimentation. However, the specification does not require that the ordinarily skilled person carries out this task. The applicants themselves have identified and elucidated the fragments containing epitopes, as SEQ ID NOs:2-4, and the claims reflect the same. No further experimentation on the part of the artisan is required in order to make and use the claimed invention.

The Examiner has suggested that antibody stimulation and binding are sensitive to amino acid changes and the like, which is correct. However, it is also known that relatively small fragments may be protective. Examples of such fragments of the botulinum A toxin for example are discussed for example by Rosenberg et al. Immunol. Invest. 1997 Jun 26(4):491-504 and Bavari et al., Vaccine 1998 Nov. 16 (19) 1850-6 (see, attached Abstracts). These papers clearly demonstrate that in relation to botulinum toxins, small fragments may be immunodominant.

The applicants have, in the specification, clearly recited certain sequences of the F toxin that are required for protective effect on the basis of their detailed knowledge and understanding of the botulinum toxin. The reader is not invited or required to look for yet smaller sequences, as is apparently the concern of the Examiner. Withdrawal of the Section 112, first paragraph, rejection of claims 12, 17, 19 and 21 is requested.

The Section 112, second paragraph, rejection of claims 28 and 30 stated in paragraph 8 of Paper No. 29 is moot in view of the above. Withdrawal of the Section 112, second paragraph rejection of claims 28 and 30 in view of the above is requested.

The Section 102 rejection of claim 13 over Campbell (Journal of Clinical Microbiology, 31, 2255-2262, 1993 and Genbank Accession No. X70821) is traversed.

Reconsideration and withdrawal of the rejection are requested as the reference apparently discloses a sequence extending from positions 623-1017 (see, page 2257, second column, second paragraph) which appears only to be part relevant to claims which recite the inclusion of sequences that encode SEQ ID NO:2 of the present application. Claim 13 is believed to be patentable over the art and withdrawal of the rejection is requested.

The Section 102 rejection of claims 5 and 13 over Elmore (Genbank Accession No. L35496) is obviated by the above amendments, which define the presently claimed invention as including polypeptides of no more than 700 amino acids. The cited reference is believed to disclose a full-length sequence which does not anticipate or make obvious the presently claimed invention. Withdrawal of the Section 102 rejection of claims 5 and 13 over Elmore is requested.

The Section 102 rejection over Wadsworth (Biochem. Journal 268:123-128, 1990) is obviated by the above as Wadsworth describes isolation of the full-length toxin and separation of the heavy chain which is believed to be 838 amino acids long (see, Figure 1 of the present application). The presently claimed invention is novel and patentable over Wadsworth. Withdrawal of the Section 102 rejection of claims 5-7 over Wadsworth is requested.

The Section 102 rejection of claims 5, 7, 12 and 32 over Hathewaw (Applied and Environmental Microbiology, 31(2):234-242, 1976) should be withdrawn as the art is submitted to relate to a full-length toxin, which fails to anticipate or make obvious the presently claimed invention. Withdrawal of the Section 102 rejection of claims 5, 7 and 32 over Hathewaw is requested.

The Section 103 rejection of claims 8-11, 14 and 17, 19, 21, 25, 26, 30, 31 and 33 over Campbell, Elmore, Wadsworth, Hathewaw and Kink (U.S. Patent No. 5,736,139) is traversed. Reconsideration and withdrawal of the rejection are requested as, noted above, the primary references all relate to full-length sequences which, alone or combined with Kink, fail to teach or suggest the presently claimed invention. While Kink may refer to fusion proteins including the purification elements relating to the same, the secondary reference fails to cure the deficiencies of the previously discussed primary references. Accordingly, the claims are submitted to be patentable over the cited combination of art. Withdrawal of the Section 103 rejection is requested.

In view of the above and attached, the claims are submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION

Amend the specification as follows.

Page 10, delete the paragraph spanning lines 16-18 and insert the following therefor:

--**Figure 3:** shows an example of a recombinant plasmid (pFHC206) made in which the synthetic DNA fragment of Figure 5 is inserted into the expression plasmid pMal-C2; (SEQ ID NOs:7 (DNA) and 8 (amino acid) and--

IN THE CLAIMS

5. (Five Times Amended) An isolated polypeptide comprising a sequence of no more than 700 consecutive amino acids of a type F botulinum toxin sequence, which comprises a sequence of amino acids selected from the group consisting of:

(a) amino acids 848-1278 of a type F botulinum toxin (SEQ ID NO: 1)

(b) [amino acids 848-991 of a type F botulinum toxin (SEQ ID NO: 2)

(c)] amino acids 992-1135 of a type F botulinum toxin (SEQ ID NO: 3), and;

[(d)] (c) amino acids 1136-1278 of a type F botulinum toxin (SEQ ID NO: 4).

6. (Five Times Amended) An isolated polypeptide comprising a dimer of a polypeptide comprising no more than 700 consecutive amino acids of a type F botulinum

toxin sequence, which comprises a sequence [of the sequences] selected from the group consisting of:

(a) amino acids 848-1278 of a type F botulinum toxin (SEQ ID NO: 1)

(b) amino acids 848-991 of a type F botulinum toxin (SEQ ID NO: 2)

(c) amino acids 992-1135 of a type F botulinum toxin (SEQ ID NO: 3), and

(d) amino acids 1136-1278 of a type F botulinum toxin (SEQ ID NO: 4).

7. (Five Times Amended) A polypeptide composition comprising:

(1) an isolated polypeptide according to claim 5; and

(2) an isolated polypeptide that facilitates or enhances purification of the polypeptide of (1)[composition].

8. (Four Times Amended) An isolated fusion protein comprising [A polypeptide composition comprising an isolated fusion protein of] a sequence of amino acids selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID and NO:4, fused to a polypeptide that facilitates or enhances purification [of the composition].

9. (Three Times Amended) A fusion protein [polypeptide composition] according to Claim [7]8 wherein said [isolated] polypeptide that facilitates or enhances purification [of the composition] is a polypeptide that binds a chromatography column.

10. (Three Times Amended) A fusion protein [polypeptide composition] according to Claim 9 wherein said chromatography column is an affinity chromatography column.

11. (Twice Amended) A fusion protein [polypeptide] according to Claim 8 which comprises SEQ ID NO:1 fused to [comprising a fusion protein of: -

(a) amino acids 848 to 1278 of a type F botulinum neurotoxin (SEQ ID NO:1), with

(b)]a purification moiety.

12. (Four Times Amended) A vaccine comprising a pharmaceutically acceptable carrier and a polypeptide comprising no more than 700 consecutive amino acids of a type F botulinum toxin sequence, which comprises a sequence selected from the group consisting of: [according to claim 5]

(a) amino acids 848-1278 of a type F botulinum toxin (SEQ ID NO:1),

(b) amino acids 848-991 of a type F botulinum toxin (SEQ ID NO:2),

(c) amino acids 992-1135 of a type F botulinum toxin (SEQ ID NO:3), and

(d) amino acids 1136-1278 of a type F botulinum toxin (SEQ ID NO:4).

13. (Three Times Amended) A recombinant DNA encoding a polypeptide according to claim 5[3].

14. (Three Times Amended) A method of producing a polypeptide according to claim [3]8 comprising the steps of:

(a) expressing in a host cell a DNA encoding a fusion protein according to claim 8, [said protein being a fusion of (i) a fragment or derivative of a type F botulinum toxin, and (ii) a moiety adapted to bind to a chromatography column,]

(b) obtaining from said host cell an extract comprising the fusion protein, and

(c) purifying the fusion protein using a chromatography column.

17. (Three Times Amended) A method of making a pharmaceutical composition comprising:

(a) expressing in a host cell a DNA fragment encoding a fusion protein according to claim 8, [said protein being a fusion of (i) a polypeptide free of toxin activity and capable of inducing protective immunity against a botulinum toxin, and (ii) a purification moiety that binds to a chromatography column,]

(b) obtaining from said host cell an extract comprising the fusion protein,

(c) purifying the fusion protein using chromatography column,

(d) incorporating the purified fusion protein into a pharmaceutical composition.

19. (Four Times Amended) A pharmaceutical composition comprising[:

(a)] a fusion protein according to claim 8, [said protein being a fusion of (i) a polypeptide as described in claim 5, and (ii) a polypeptide that binds to a chromatography column;] and

[(b)] a pharmaceutically acceptable carrier.

25. (Amended) A recombinant DNA encoding a fusion protein according to claim 8 [polypeptide composition according to claim 7].

30. (Three Times Amended) The fusion protein of claim [26]8 wherein (1) is [said amino acid sequence comprises] at least one amino acid sequence selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 3, and SEQ ID NO: 4.

33. (Amended) A method of producing antibodies in a mammal against botulinum toxin, comprising administering to said mammal a composition of claim [31]19.